PTPsigma inhibitors promote hematopoietic stem cell regeneration.

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Authors: Yurun Zhang, Martina Roos, Heather Himburg, Christina M Termini, Mamle Quarmyne, Michelle Li, Liman Zhao, Jenny Kan, Tiancheng Fang, Xiao Yan, Katherine Pohl, Emelyne Diers, Hyo Jin Gim, Robert Damoiseaux, Julian Whitelegge, William McBride, Michael E Jung, John P Chute

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Public Summary:
We have discovered a receptor protein that is expressed by blood stem cells called PTP-sigma. This receptor inhibits blood stem cell expansion and recovery from injury. We developed a new class of drugs that specifically inhibit PTP-sigma on blood stem cells and cause the accelerated recovery of blood stem cells in mice following irradiation or chemotherapy treatment. This same treatment also causes human blood stem cells to regenerate faster following radiation exposure. These new drugs that inhibit PTP-sigma have the potential to accelerate human blood system recovery and human blood stem cell regeneration in patients who have received chemotherapy, radiation treatment or bone marrow transplantation.

Scientific Abstract:
Receptor type protein tyrosine phosphatase-sigma (PTPsigma) is primarily expressed by adult neurons and regulates neural regeneration. We recently discovered that PTPsigma is also expressed by hematopoietic stem cells (HSCs). Here, we describe small molecule inhibitors of PTPsigma that promote HSC regeneration in vivo. Systemic administration of the PTPsigma inhibitor, DJ001, or its analog, to irradiated mice promotes HSC regeneration, accelerates hematologic recovery, and improves survival. Similarly, DJ001 administration accelerates hematologic recovery in mice treated with 5-fluorouracil chemotherapy. DJ001 displays high specificity for PTPsigma and antagonizes PTPsigma via unique non-competitive, allosteric binding. Mechanistically, DJ001 suppresses radiation-induced HSC apoptosis via activation of the RhoGTPase, RAC1, and induction of BCL-XL. Furthermore, treatment of irradiated human HSCs with DJ001 promotes the regeneration of human HSCs capable of multilineage in vivo repopulation. These studies demonstrate the therapeutic potential of selective, small-molecule PTPsigma inhibitors for human hematopoietic regeneration.